B2 A26

(19) Europäisches Patentamt
European Patent Office
Office europé n d s br vets

(11) Publication number: **0 345 592 A1**

(12) **EUROPEAN PATENT APPLICATION** for 09/445,193

(21) Application number: 89109676.0

(22) Date of filing: 30.05.89

(51) Int. Cl.⁴: **C07D 307/79 , C07D 307/92 , C07D 405/12 , //A61K31/34**

NEW 2-SUBSTD. COUMARAN DERIVS. INHIBIT 5-LIPOXYGENASE + USEFUL AS CENTRAL NERVOUS SYSTEM AGENTS, CIRCULATORY AGENTS & OR ANTI-ALLERGIC AGENTS.

(30) Priority: 10.06.88 JP 143860/88

(43) Date of publication of application: 13.12.89 Bulletin 89/50

(84) Designated Contracting States: AT BE CH DE ES FR GB GR IT LI LU NL SE

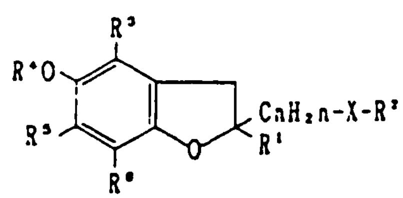
(71) Applicant: TAKEDA CHEMICAL INDUSTRIES, LTD.
3-6, Doshomachi 2-chome Chuo-ku
Osaka 541(JP)

(72) Inventor: Goto, Giichi
6-11, Kofudai 5-chome Toyono-cho
Toyono-gun Osaka 563-01(JP)
Inventor: Ohkawa, Shigenori
45-20, Makamicho 6-chome
Takatsuki Osaka 569(JP)
Inventor: Fukuda, Naohisa
1-56, Suimeidai 4-chome
Kawanishi Hyogo 666-01(JP)

(74) Representative: Lederer, Franz, Dr. et al
Van der Werth, Lederer & Riederer
Patentanwälte Lucile-Grahn-Strasse 22
D-8000 München 80(DE)

(54) **Novel 2-substituted coumaran derivatives.**

(57) The present invention relates to a compound of the formula:



(I)

wherein R^1 stands for hydrogen or a lower alkyl; n denotes an integer of 1 to 6; X stands for an optionally oxidized sulphur atom, oxygen atom or an optionally substituted imino; R^2 stands for m thyl or an organic residual group bonded through methylene, methine a quaternary carbon; R^3 stands for a lower alkyl; R^4 stands for hydrogen or acyl; R^5 and R^6 each stand for a lower alkoxy or a lower alkyl, or R^5 and R^6 combinedly stand for butadienylene, and salts thereof.

The compound (I) of the present invention has a strong 5-lipoxygenase inhibiting action, is of high safety and is useful as, among others, an agent for ameliorating circulatory system, an anti-allergic agent and a pharmaceutical agent for central nervous system.

EP 0 345 592 A1

489 89365389

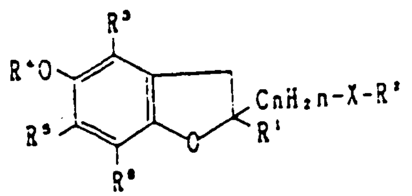
Novel 2-Substituted Coumaran Derivatives

This invention relates to novel 2-substituted coumaran derivatives.

While several types of compounds of coumaran derivatives have been synthesized [Journal of American Chemical Society (J. Am. Chem. Soc.) 105, 5950(1983); ibid, 107, 7053(1985)], substantially no reports have been made on th ir pharmacological actions.

The present inventors synthesized various types of coumaran derivatives and found that they had inhibitory actions on 5-lipoxygenase participating in the biosynthesis of leucotrienes and lipoxins, and they have continued the research work diligently to accomplish the present invention.

This invention is to provide a compound represented by the formula:



(I)

wherein R^1 stands for hydrogen or a lower alkyl; n denotes an integer of 1 to 6; X stands for an optionally oxidized sulphur atom, oxygen atom or an optionally substituted imino; R^2 stands for methyl or an organic residual group bonded through methylene, methine or a quaternary carbon; R^3 stands for a lower alkyl; R^4 stands for hydrogen or acyl; R^5 and R^6 each stand for a lower alkoxy or a lower alkyl, or R^5 and R^6 combined stand for butadienylene, and salts thereof.

Referring to the compounds represented by the formula (I), the lower alkyl shown by R^1 is exemplified by C_{1-6} alkyl such as methyl, ethyl, propyl, i-propyl, butyl, i-butyl, sec-butyl, t-butyl, amyl, hexyl, etc., and especially preferable ones are C_{1-3} alkyl (methyl, ethyl, propyl, i-propyl, etc.).

As the groups shown by C_nH_{2n}, mention is made of methylene or straight-chain or branched alkylene.

As the optionally oxidized sulfur atom shown by X, mention is made of sulfide, sulfoxide and sulfone. As the substituents of imino group, mention is made of aryl such as phenyl, naphthyl, etc. and lower (C_{1-3}) alkyl such as methyl, ethyl, propyl, i-propyl, etc.

Examples of methyl and an organic residual groups bonded through methylene, methine or quaternary carbon shown by R^2 include straight-chain or branched C_{1-10} chain-like aliphatic hydrocarbon groups such as alkyl, alkenyl, alkynyl, etc., C_{3-7} cyclic hydrocarbon groups (e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclopentynyl, cyclohexyl, cyclohexenyl, cyclohexedienyl, cycloheptynyl, etc.), aryl (e.g. phenyl, naphthyl, etc.), aralkyl (e.g. C_{1-3} alkylphenyl, C_{1-3} alkylnaphthyl, etc., such as benzyl, phenethyl, phenylpropyl, a- or b-naphthylmethyl, etc.), and non-aromatic or aromatic 5- to 7-membered monocyclic or condensed poly-cyclic heterocyclic groups (e.g. thienyl, pyridyl, imidazolyl, thiazolyl, pyrrolyl, piperidyl, hexamethylenimidyl, quinolyl, quinuclidyl, indolyl, pyrimidyl, etc.). The above-mentioned methyl or organic residual groups may have a substituent exemplified by hydroxyl group, carboxyl, C_{1-3} alkoxycarbonyl, amino, nitro, cyano, halogen (e.g. fluorine, chlorine, bromine, iodine), C_{1-3} alkoxy, C_{1-3} alkyl, aryl (e.g. phenyl, naphthyl, etc., and these groups may have any of the above-mentioned substituents), C_{3-6} cycloalkyl, heterocyclic groups (e.g. those as mentioned above), etc. When the above-mentioned organic residual groups are alkenyl, they have usually 1 to 5 double bonds optionally conjugated. When they are alkynyl, they have 1 to 5 triple bonds.

Examples of the lower alkyl shown by R^3 include C_{1-6} alkyl such as methyl, ethyl, propyl, i-propyl, butyl, i-butyl, sec-butyl, amyl, hexyl, etc., especially C_{1-3} alkyl (methyl, ethyl, propyl, i-propyl, etc.) being pref rable.

As the acyl shown by R^4, mention is made of carboxylic acid acyl, sulfonic acid acyl, phosphoric acid acyl, etc., preferably those having C_{1-6} substituents (methyl, ethyl, propyl, phenyl, etc.). Especially preferable ones include chain-like (C_{1-10}) or cyclic (C_{3-10}) alkanoyl, such as formyl, acetyl, propionyl, isobutylyl, decanoyl, cyclopentoyl or benzoyl, optionally quaterized nicotinoyl, succinic acid half-acyl, etc.

Examples of lower alkyls shown by R^5 and R^6 include C_{1-6} alkyl such as methyl, ethyl, propyl, i-propyl, butyl, i-butyl, sec-butyl, t-butyl, amyl, hexyl, etc., especially C_{1-3} alkyl (methyl, ethyl, propyl, i-propyl, etc.) being preferabl . These lower alkyl groups may have a substituent exemplified by hydroxyl group, halogen (fluorine, bromine, chlorin , iodine, etc.), nitro, trifluoromethyl, carboxyl, C_{1-3} alkoxycarbonyl

490

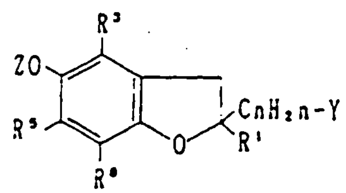
80365389

(methoxycarbonyl, ethoxycarbonyl, etc.), 3-pyridyl, 1-imidazolyl, 5-thiazolyl, etc. And, as the lower alkoxy shown by R^5 and R^6, mention is made of C_{1-4} alkoxy such as methoxy, ethoxy, propoxy, i-propoxy, butoxy, etc.

When R^5 and R^6, taken together, stand for butadienylene, they form naphthalene ring, and, as the substituents on thus-formed benzene ring, mention is made of one to three of lower (C_{1-3}) alkyls, lower (C_{1-3}) alkoxy (methoxy, ethoxy, propoxy, etc.), hydroxyl group, nitro, halogen, etc.

The compound (I) may, depending on the kinds of substituents thereon, form salts, for example, salts with acids exemplified by organic acids (e.g. acetic acid, propionic acid, oxalic acid, maleic acid, etc.) or inorganic acid (e.g. hydrochloric acid, sulfuric acid, phosphoric acid, etc.), or salts with bases exemplified by alkali metals (potassium, sodium, etc.), alkaline earth metals (calcium, magnesium, etc.), ammonia, etc., especially physiologically acceptable ones being preferable.

A compound (I), when X is sulfur atom or oxygen atom, can be produced by subjecting a compound represented by the formula:

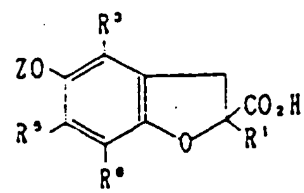


(II)

wherein R^1, R^3, R^5, and R^6 are of the same meaning as defined above, Y stands for a leaving group and Z stands for hydrogen or a hydroxyl-protecting group, and a compound represented by the formula:

$H\text{-}X\text{-}R^2$ (III)

wherein X and R^2 are of the same meaning as defined above, to substitution reaction, or a compound (I), when X is imino group, can be produced by subjecting a compound by the formula:



(II')

wherein R^1, R^3, Z, R^5 and R^6 are of the same meaning defined as above, and a compound (III) to condensation reaction by e.g. an active ester method to produce a corresponding amide compound, followed to reduction by use of e.g. lithium aluminium hydride, then when desired, to deprotection reaction, acylation or/and substituent-exchange reaction.

Examples of the above-mentioned Z include C_{1-5} alkanoyl, and those of Y include halogen, phenyl or an alkyl sulfonic acid residual group.

The substitution reaction is carried out in a solvent such as dimethylformamide, tetrahydrofuran, methanol, ethanol, etc. in the presence of a base such as sodium hydride, potassium carbonate, sodium alcoholate, triethylamine, pyridine, etc. The reaction temperatures usually range from -20°C to 80°C, and the reaction time ranges from about 0.5 to 24 hours.

While hydrolysis of acyl group can be carried out under conventional ester-hydrolysis conditions, when the product is basic and unstable to oxygen, the reaction is conducted under argon atmosphere to thereby obtain the desired hydrolyzate in a good yield.

And, when the double bond is hydrogenated, the desired compound can be obtained by, employing a catalyst such as palladium-carbon, a conventional method.

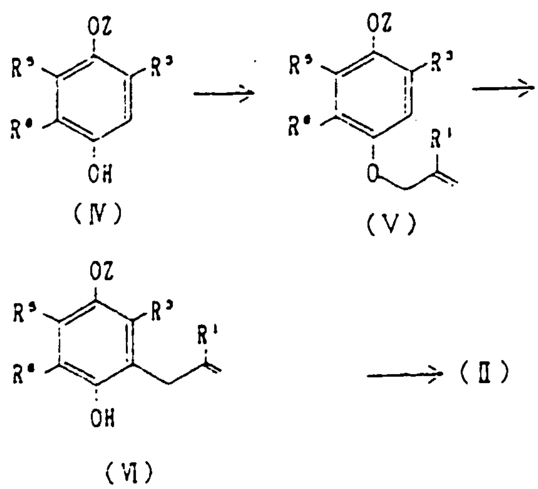
The acylation is conducted, by employing a desired acylating agent (e.g. acid anhydride, acid halide), in an organic solvent (e.g. dim thylformamide, acetone, tetrahydrofuran), when necessary, in the presence of a basic catalyst (preferably a base such as sodium hydride, potassium carbonate, pyridine or triethylamine) or an acid catalyst (sulfuric acid, hydrogen chloride, etc.). The reaction temperatures range from about -10°C to 100°C, and the reaction time ranges from about 10 minutes to 15 hours.

Thus-obtained compound (I) can be isolated by a conventional separation purification means (extraction, chromatography, recrystallization, etc.).

Incidentally, when the compound (I) exists as a diastereomer, it can be isolated into the respective isomers when desired.

And, when the compound (I) is an optionally active one, it can be separated into d-isomer and ℓ-isomer by a conventional optical resolution means.

The starting compound (II) can be synthesized by, for example, the following method. Namely, a hydroquinone monoacetate (IV) is allowed to react, in the presence of a base, with aryl halogenide to give an allylether (V), and (V) is led to (VI) by Claisen rearrangement. Further, (VI) is processed with bromine in the presence of a base to obtain the compound (II) as a bromomethyl compound.



The compound (I) of this invention has an action of inhibiting production of 5-lipoxygenase-type metabolite [leucotrienes, 5-hydroperoxyeicosatetraenoic acid (HPETE), 5-hydroxyeicosatetraenoic acid (HETE), lipoxins, leucotoxins, etc., and therefore, it can be used advantageously as an agent acting on central nervous system, an agent for ameliorating circulatory system, an anti-allergic agent, etc.

The compound (I) can be safely administered, orally or non-orally, singly or as a pharmaceutical composition prepared by mixing the compound (I) with a per se known pharmaceutically acceptable carrier, excipient, etc. (e.g. tablet, capsule, liquid, injection, suppository,, to mammals (rat, horse, cow, monkey, human, etc.). While the dosage varies with subjects of administration, administration routes, symptoms, etc., in the case of, for example, administering orally to an adult patient suffering from diseases of circulatory system, it is convenient to administer with about 0.1 mg/kg to 20 mg/kg/body weight/dose, preferably 0.2 mg/kg to 10 mg/kg/body weight, once to three times a day.

Experimental Example 1 5-Lypoxygenase Inhibiting Action

In 0.5 mℓ of MCM (mast cell medium) was suspended 10^7 of rat basophilic leukemia (RBL-1) cells. To this suspension was added the test solution previously prepared [consisting of 0.5 mℓ of MCM, 50 µg of arachidonic acid, 10 µg of calcium ionophore A-23187 and the test compound (final concentrations 10 µM, 1 µM, 0.1 µM and 0.01 µM], and the reaction was allowed to proceed at 37°C for 20 minutes. To the reaction mixture was added 4 mℓ of ethanol, which was shaken sufficiently, followed by leaving the resultant mixture standing for 10 minutes at room temperatures. The resultant mixture was subjected to centrifuge (2000 rpm) for 10 minutes, then the supernatant was separated. Thus-separated supernatant was concentrated to dryness under reduced pressure. To the concentrate was added 0.5 mℓ of a 60% aqueous methanol. 100 µℓ portion of this solution was taken and subjected to high performance liquid chromatography to determine 5-HETE (5-hydroxyeicosatetraenoic acid) quantitatively. UV absorption of 5-HETE at 237 nm was measured with a UV absorption monitor. The inhibitory effect (IE) of 5-HETE is expressed by (1-b/a) x 100. In this formula, a means the height of the peak or the area of the peak in the case of containing no compound (I), while b means the height of the peak or the area of th peak in the case of containing the compound (I). The results revealed, as shown in Table 1, that the test compounds showed strong inhibitory action on the production of 5-HETE.

492

89365389

Table 1

Effect of Inhibiting 5-Lipoxygenase				
	% Inhibition (IE)			
Compound	10^{-5}M	10^{-6}M	10^{-7}M	10^{-8}M
1	100	100	64	13
3	100	100	100	42
5	100	100	48	24
7	100	100	45	-
9	100	100	96	8
11	100	100	19	-
13	100	100	8	-
15	100	100	19	10
17	100	100	88	-
19	100	99	87	-5
21	100	100	98	18
25	95	99	94	14

Examples

By the following Reference Examples, Examples and Formulation Examples of the compounds of the present invention, the present invention will be described in a more concrete manner, but the present invention is not to be limited thereto.

Reference Example 1

To a solution of 4-acetoxy-2,3,5-trimethylphenol [20 g (103 mmol)] and methallyl chloride [10 g (110.4 mmol.)] in dimethylformamide (160 mℓ) was added potassium carbonate [15.2 g (110 mmol.)]. The mixture was stirred for 3 hours at 80 °C under argon atmosphere. The reaction mixture was, after cooling, diluted with water, which was subjected to extraction with ethyl acetate. The extract was washed with water and dried, then the solvent was distilled off. The residue was crystallized from hexane to obtain the desired 4-acetoxy-2,3,5-trimethylphenyl-2-methylpropenyl ether [18.5 g (yield 72.4%)], m.p.44 ° to 45 °C.

In a manner similar to the above, 4-acetoxy-2,3,5-trimethylphenyl allyl ether was synthesized. (Yield 76.7%, m.p. 40 ° to 41 °C).

Reference Example 2

In N,N-diethylaniline (100 mℓ) was dissolved 4-acetoxy-2,3,5-trimethylphenyl 2-methylpropenylether [16.2 g (6.5 mmol)], which was heated at 200 °C for two hours. The reaction mixture was cooled and diluted with isopropyl ether, which was washed with 2N-HCℓ to remove N,N-diethylaniline. The remainder was washed with a saturated aqueous solution of sodium hydrogencarbonate, which was dried, followed by distilling off the solvent. The residue was crystallized from isopropylether-hexane to obtain the desired 4-acetoxy-2-(2-methyl-2-propenyl)- 3,4,6-trimethylphenol [14.9 g (yield 91.7%)], m.p. 109 -110 °C.

In a manner similar to the above, 4-acetoxy-2-allyl-3,4,6-trimethylphenol was synthesized. (Yield 94.6%, m.p. 117 °-118 °C).

Reference Example 3

To a chloroform (15 mℓ) solution of 4-acetoxy-2-allyl-3,5,6-trimethylphenol [2.0 g (8.5 mmol)] was added dropwise, while stirring, bromine [1.36 g (8.5 mmol)]. To the mixture was then added triethylamine (0.3 mℓ., which was heated for two hours under reflux. The reaction mixture was cooled, washed with water,

dried and then concentrated. The concentrate was crystallized from hexane to obtain 5-acetoxy-2-bromomethyl-4,6,7-trimethyl-2,3-dihydrobenzofuran [2.5 g (yield 93.2%)].

In a manner similar to the above, 5-acetoxy-2-bromomethyl-2,4,6,7-tetramethyl-2,3-dihydrobenzofuran was obtained from 4-acetoxy-3,5,6-trimethyl-2-(2-methyl-2-propenyl)phenol.

Example 1

To a solution of thiophenol [425 mg (3.8 mmol)] in dimethylformamide (10 mℓ) was added, under ice-cooling, sodium hydride [167 mg (4.2 mmol, content:60%)]. To the reaction mixture was added, after stirring for 20 minutes, a solution of 5-acetoxy-2-bromomethyl-4,6,7-trimethyl-2,3-dihydrobenzofuran [1.2 g (3.8 mmol)] in dimethylformamide (5 mℓ). The mixture was stirred for further 30 minutes. The reaction mixture was diluted with water, which was subjected to extraction with ethyl acetate. The extract solution was washed with water, dried and concentrated. The concentrate was crystallized from isopropylether-hexane to afford 5-acetoxy-4,6,7-trimethyl-2-phenylthiomethyl-2,3-dihydrobenzofuran (Compound 4) [1.2 g (yield : 91.3%)]. In a manner similar to the above, compounds 2, 6, 8, 10, 12 and 18 were synthesized by mploying the corresponding thio compounds (3-mercaptopropionic acid, 1-octanethiol, 2-mercaptopyridine, 4-fluorothiophenol, 2-naphthalene thiol and benzyl mercaptan). Incidentally, when 3-mercaptopropionic acid is employed as the starting compound, 2.2 equivalents of sodium hydride was used.

Example 2

To a solution of 5-acetoxy-2-(phenylthiomethyl)-4,6,7-trimethyl-2,3-dihydrobenzofuran [1.2 g (3.5 mmol)] in methanol (8 mℓ) was added a solution of sodium hydroxide (0.6 g) in water (5 mℓ). The mixture was heated for one hour under reflux under argon atmosphere. The reaction mixture was, after cooling, diluted with water and, then, neutralized with 2N-HCℓ, followed by extraction with ethyl acetate. The extract solution was washed with water, which was dried, then the solvent was distilled off. The residue was crystallized from isopropyl ether-hexane to obtain 5-hydroxy-2-phenylthiomethyl)-4,6,7-trimethyl-2,3-dihydrobenzofuran (Compound 3) (0.85 g).

In a manner similar to the above, compounds 1, 5, 7, 9, 11, 13, 15 and 17 were synthesized by employing the corresponding 5-acetoxy compounds (Compounds 2, 6, 8, 10, 12, 14, 16 and 18).

Example 3

To a solution of 5-acetoxy-2-(phenylthiomethyl)-4,6,7-trimethyl-2,3-dihydrobenzofuran (1.0 g) in methanol (10 mℓ) was added a 1M aqueous solution of sodium periodate (10 mℓ), and the mixture was stirred at room temperatures for three hours. The reaction mixture was diluted with water, and the reaction product was extracted with ethyl acetate. The extract solution was washed with water and dried, and then the solvent was distilled off. The residue was crystallized from ethyl acetate - isopropyl ether to obtain desired 5-acetoxy-2-(phenylsulfinylmethyl)-4,6,7-trimethyl-2,3-dihydrobenzofuran (Compound 14) (0.72 g).

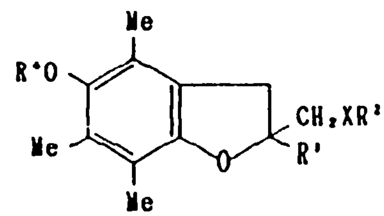
Example 4

To a solution of 5-acetoxy-2-(phenylthiomethyl-4,6,7-triethyl-2,3-dihydrobenzofuran (1.0 g) in methanol (10 mℓ) was added a 2M aqueous solution of periodate (10 mℓ). The mixture was heated for 14 hours under reflux. The reaction mixture was, after cooling, diluted with water. The reaction product was extracted with ethyl acetate. The extract was washed with water, which was dried, and then the solvent was distilled off. The residue was crystallized from isopropyl ether-ethyl acetate to obtain 1.0 g of the desired 5-acetoxy-2-(phenylsulfonyl)-4,6,7-trimethyl-2,3-dihydrobenzofuran (Compound 16).

The physico-ch mical properties of the compounds obtained above are shown in Tabl 2.

494

Table 2



Compd. No.	R¹	X	R²	R⁴	Yield (%)	m.p. (℃)	NMR (δ ppm) CDCℓ₃中
1	H	S	$-(CH_2)_2CO_2H$	H	87.3	132-133	2.10(9H), 2.50-3.30(8H), 4.85(1H), 5.10(2H); in DMSO-d_6
2	H	S	$-(CH_2)_2CO_2H$	Ac	61.9	126-127	1.97(6H), 2.07(3H), 2.30(3H), 2.50-3.50(8H), 5.15(1H), 11.00(1H) ; in DMSO-d_6
3	H	S	Ph-	H	81.2	108-109	2.07(3H), 2.13(6H), 2.80-3.10(4H), 4.17(1H), 4.85(1H), 7.20-7.50(5H)
4	H	S	Ph-	Ac	91.3	77-78	1.97(6H), 2.07(3H), 2.30(3H), 2.80-3.50(4H), 4.90(1H), 7.20-7.50(5H)

495

89365389

5	H	S	$-(CH_2)_7CH_3$	H	80.4	84- 85	1.20(3H), 1.20-1.70(10H), 2.10(9H), 2.20-3.20(6H), 4.13(1H), 4.83(1H)
6	H	S	$-(CH_2)_7CH_3$	Ac	73.7	—	0.87(3H), 1.10-1.70(10H), 1.97(6H), 2.07(3H), 2.30(3H), 2.30-3.30(6H), 4.90(1H)
7	H	S	2-Py-	H	57.0	141-142	2.10(9H), 2.90-3.80(4H), 4.17(1H), 5.00(1H), 6.95(1H), 7.20(1H), 7.45(1H), 8.38(1H)
8	H	S	2-Py-	Ac	85.4	91- 92	1.97(6H), 2.07(3H), 2.30(3H), 2.95(1H), 3.27(1H), 3.38(1H), 3.67(1H), 5.05(1H), 6.95(1H), 7.17(1H), 7.45(1H), 8.40(1H)
9	H	S	4-F-Ph-	H	64.8	123-124	2.03(3H), 2.10(6H), 2.80-3.40(4H), 4.13(1H), 4.83(1H), 6.97(2H), 7.42(2H)
10	H	S	4-F-Ph-	Ac	86.7	118-119	2.00(9H), 2.30(3H), 2.80-3.40(4H), 4.90(1H), 6.97(2H), 7.42(2H)
11	H	S	2-Nap-	H	75.0	114-115	2.00(3H), 2.10(6H), 3.00-3.60(4H), 4.15(1H), 4.93(1H), 7.35-7.60(3H), 7.65-7.90(4H)

496

89365389

12	H	S	2-Nap-	Ac	63.8	106-107	2.00(9H), 2.30(3H), 3.00-3.60(4H), 4.95(1H), 7.35-7.60(3H), 7.65-7.90(4H)
13	H	SO	Ph-	H	84.9	150-152	2.10(9H), 2.70-3.50(4H), 4.50(1H), 4.70-5.40(1H), 7.45-7.80(5H)
14	H	SO	Ph-	Ac	68.8	—	2.00(9H), 2.70-3.50(4H), 4.80-5.50(1H), 7.40-7.80(5H)
15	H	SO_2	Ph-	H	84.9	161-162	1.77(3H), 2.07(6H), 2.70-3.80(5H), 5.15(1H), 7.45-7.75(3H), 7.90-8.10(2H)
16	H	SO_2	Ph-	Ac	91.5	154-155	1.73(3H), 1.92(3H), 1.95(3H), 2.28(3H), 2.70-3.80(4H), 5.20(1H), 7.40-7.70(3H), 7.90-8.10(2H)
17	H	S	$-CH_2Ph$	H	95.3	93- 94	2.13(9H), 2.50-3.30(4H), 3.80(2H), 4.13(1H), 4.83(1H), 7.20-7.40(5H)
18	H	S	$-CH_2Ph$	Ac	82.8	97- 98	1.97(6H), 2.08(3H), 2.30(3H), 2.50-3.30(4H), 3.80(2H), 4.87(1H), 7.20-7.40(5H)
19	Me	S	Ph-	H	83.8	88- 89	1.53(3H), 2.00(3H), 2.07(3H), 2.10(3H), 2.85(1H), 3.20(1H), 3.23(2H), 4.10(1H), 7.10-7.40(5H)

497

89365389

20	Me	S	Ph-	Ac	98.0	oil	1.55(3H), 1.95(3H), 1.99(6H), 2.33(3H), 2.90(1H), 3.20(1H), 3.27(2H), 7.10-7.40(5H)
21	Me	S	4-F-Ph-	H	87.2	82-83	1.50(3H), 1.97(3H), 2.07(3H), 2.10(3H), 2.85(1H), 3.17(2H), 3.20(1H), 4.10(1H), 6.90(2H), 7.32(2H)
22	Me	S	4-F-Ph-	Ac	98.0	oil	1.52(3H), 1.95(6H), 1.97(3H), 2.30(2H), 2.87(1H), 3.20(3H), 6.90(2H), 7.32(2H)
23	Me	O	$-CH_2Ph$	H	73.3	80-81	1.47(3H), 2.12(3H), 2.17(3H), 2.20(3H), 4.48(1H), 3.17(1H), 3.52(1H), 3.75(1H), 4.73(2H), 7.30-7.65(5H)
24	Me	O	$-CH_2Ph$	Ac	54.0	71-72	1.47(3H), 2.03(3H), 2.07(3H), 2.13(3H), 2.17(3H), 2.83(1H), 3.10(1H), 4.13(2H), 4.68(2H), 7.25-7.55(5H)
25	Me	NH	$-(CH_2)_2Ph$	H	82.3	74-75	1.42(3H), 2.07(6H), 2.13(3H), 2.60-3.25(9H), 4.20(1H), 7.23(5H)

Ph: Phenyl, Py: Pyridyl, Ac: Acetyl, Nap: Naphthyl

498

Formulation Example

Capsule

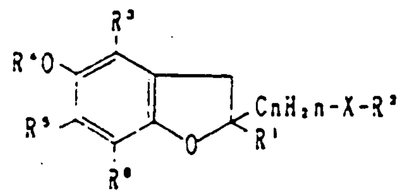
89365389

(1)	Compound 3	50 mg
(2)	Finely pulverized cellulose	30 mg
(3)	Lactose	37 mg
(4)	Magnesium stearate	3 mg
	Total	120 mg

(1), (2), (3) and (4) were mixed, which was filled in a gelatine capsule.

Claims

1. A compound of the formula:



wherein R^1 stands for hydrogen or a lower alkyl; n denotes an integer of 1 to 6; X stands for an optionally oxidized sulphur atom, oxygen atom or an optionally substituted imino; R^2 stands for methyl or an organic residueal group bonded through methylene, methine or a quaternary carbon; R^3 stands for a lower alkyl; R^4 stands for hydrogen or acyl; R^5 and R^6 each stand for a lower alkoxy or a lower alkyl, or R^5 an R^6 combinedly stand for butadienylene, or a salt thereof.

2. The compound according to claim 1, wherein R^1 is hydrogen or C_{1-6} alkyl.

3. The compound according to claim 1, wherein n is an integer of 1 to 3.

4. The compound according to claim 1, wherein X is sulfide, sulfoxide, sulfone, oxygen or imino.

5. The compound according to claim 1, wherein R^2 is C_{1-10} chain-like aliphatic hydrocarbon group, C_{3-7} cyclic hydrocarbon group, aryl, aralkyl or non-aromatic or aromatic 5 to 7 membered monocyclic or condensed polycyclic heterocyclic group, which may be substituted.

6. The compound according to claim 5, wherein R^2 is C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkenyl, phenyl, naphthyl, C_{1-3} alkylphenyl, C_{1-3} alkylnaphthyl, thienyl, pyridyl, imidazolyl, thiazolyl, pyrrolyl, piperidyl, hexamethyleneimidyl, quinoyl, quinuclidyl, indolyl or pyrimidyl, which may be substituted by hydroxy, carboxy, C_{1-3} alkoxycarbonyl, amino, nitro, cyano, halogen, C_{1-3} alkoxy, C_{1-3} alkyl, acyl, C_{3-6} cycloalkyl or heterocyclic group.

7. The compound according to claim 1, wherein R^3 is C_{1-6} alkyl.

8. The compound according to claim 1, wherein R^4 is hydrogen or C_{1-10} alkanoyl.

9. The compound according to claim 1, wherein R^5 and R^6 each is C_{1-6} alkyl.

10. The compound according to claim 1, wherein R^1 is hydrogen or C_{1-3} alkyl; n is 1; X is sulfide or oxygen; R^2 is C_{1-10} alkyl which may be substituted by halogen, carboxy or phenyl, phenyl which may be substituted by halogen or C_{1-3} alkxoy, naphthyl or pyridyl; R^3 is C_{1-3} alkyl; R^4 is hydrogen or acetyl; and R^5 and R^6 are each C_{1-3} alkyl.

11. The compound according to claim 1, which is 5-hydroxy-2-(phenylthiomethyl)-4,6,7-trimethyl-2,3-dihydrobenzofuran.

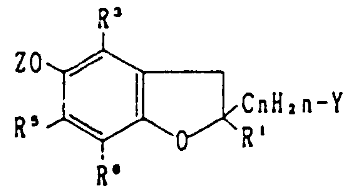
12. The compound according to claim 1, which is 5-hydroxy-2-(octylthiomethyl)-4,6,7-trimethyl-2,3-dihydrobenzofuran.

13. The compound according to claim 1, which is 5-hydroxy-2-(4-fluorophenylthiomethyl)-4,6,7-trimethyl-2, 3-dihydrobenzofuran.

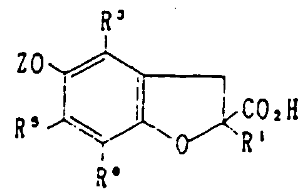
14. A method of producing the compound according to claim 1, which comprises subjecting, when X is sulfur atom or oxygen atom, a compound of the formula:

499

89365389



wherein R', R³, R⁵ and R⁶ are of the same meaning as defined above, Y is a leaving group and Z is hydrogen or hydroxy-protecting group, and a compound of the formula:
$H\text{-}X\text{-}R^2$
wherein X and R^2 are of the same meaning as defined above, to substitution reaction, or subj cting, when X is imino group, a compound of the formula:



wherein R', R^3, Z, R^5 and R^6 are of the same meaning as defined above, and a compound of the formula:
$H\text{-}X\text{-}R^2$
wher in X and R^2 are of the same meaning as defined above, to condensation reaction to produce a corresponding amide compound, followed to reduction, then when desired, to deprotection reaction, acylation or/and substituent-exchange reaction.

500

89365389

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 89 10 9676

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
Y	CHEMICAL ABSTRACTS, vol. 108, 7th March 1988, page 445, abstract no. 82107a, Columbus, Ohio, US; & JP-A-62 169 726 (YOSHITOMI PHARMACEUTICAL INDUSTRIES, LTD et al.) 25-07-1987 * Abstract * ---	1-14	C 07 D 307/79 C 07 D 307/92 C 07 D 405/12 // A 61 K 31/34
Y	CHEMICAL ABSTRACTS, vol. 110, no. 9, 27th February 1989, page 630, abstract no. 75294x, Columbus, Ohio, US; & JP-A-63 88 173 (KURARAY CO., LTD) 19-04-1988 * Abstract * -----	1-14	
			TECHNICAL FIELDS SEARCHED (Int. Cl.4)
			C 07 D 307/00 C 07 D 405/00

501

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	25-08-1989	ALLARD M.S.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0401)